Listing of Claims:

1-53. (Canceled)

54. (Previously presented) A fusion protein comprising an antigen of an influenza virus, or an antigenic portion thereof, and a stress protein, or a portion thereof, wherein the antigen of the influenza virus is nucleoprotein, neuraminidase, M1, M2, PB1, PB2, or PA and the fusion protein induces an immune response against the antigen in a mammal to whom the fusion protein is administered.

55-56. (Canceled)

57. (Previously presented) The fusion protein of claim 54, wherein the antigen of the influenza virus is nucleoprotein.

58. (Previously presented) The fusion protein of claim 54, wherein the fusion protein is encoded by plasmid pET65MP/NP-B or plasmid pET65MP/NP-D.

59. (Previously presented) The fusion protein of claim 54, wherein the antigen includes a CTL epitope.

60. (Canceled)

61. (Previously presented) A fusion protein comprising an antigen of an influenza virus, or an antigenic portion thereof, and a bacterial stress protein, or a portion thereof, wherein the antigen of the influenza virus is nucleoprotein, neuraminidase, M1, M2, PB1, PB2, or PA and the fusion protein induces an immune response against the antigen in a mammal to whom the fusion protein is administered.

62. (Previously presented) The fusion protein of claim 61, wherein the bacterial stress protein is a mycobacterial stress protein.

63. (Previously presented) A composition comprising the fusion protein of claim 54 and a pharmaceutically acceptable excipient, carrier, diluent, or vehicle.

64. (Previously presented) A method of inducing an immune response against an antigen of an influenza virus, the method comprising administering the fusion protein of claim 54 to a vertebrate in an amount effective to induce an immune response against the antigen.

65. (Previously presented) The method of claim 64, wherein the fusion protein is administered in combination with a pharmaceutically acceptable excipient, carrier, diluent, or vehicle.

66. (Previously presented) A method of inducing an immune response against an antigen of the influenza virus, the method comprising administering the fusion protein of claim 58 to a vertebrate in an amount effective to induce an immune response against the antigen.

67. (Previously presented) The method of claim 66, wherein the fusion protein is administered in combination with a pharmaceutically acceptable excipient, carrier, diluent, or vehicle.

68. (Previously presented) The fusion protein of claim 54, wherein the immune response is a cell mediated immune response.

69. (Previously presented) The fusion protein of claim 68, wherein the cell mediated immune response is a cell mediated cytolytic immune response.

70-87. (Canceled)

88. (Previously presented) The fusion protein of claim 68, wherein the cell mediated immune response is a class I-restricted T cell response.

89. (Previously presented) The fusion protein of claim 68, wherein the cell mediated immune response is a class II-restricted T cell response.

90. (Previously presented) The fusion protein of claim 59, wherein the CTL epitope is a class I-restricted T cell epitope.

91. (Previously presented) The fusion protein of claim 59, wherein the CTL epitope is a class II-restricted T cell epitope.

92. (Previously presented) The fusion protein of claim 62, wherein the stress protein is hsp65.

93. (Previously presented) The fusion protein of claim 62, wherein the stress protein is hsp71.

94. (Previously presented) The fusion protein of claim 54, wherein the stress protein is an Hsp100-200, an Hsp100, an Hsp90, Lon, an Hsp70, an Hsp60, TF55, an Hsp40, an FKBP, a cyclophillin, an Hsp20-30, ClpP, GrpE, Hsp10, ubiquitin, calnexin, or a protein disulfide isomerase.

95. (Previously presented) The method of claim 64, wherein the immune response is a cell mediated immune response.

96. (Previously presented) The method of claim 95, wherein the cell mediated immune response is a cell mediated cytolytic immune response.

97. (Previously presented) The method of claim 95, wherein the cell mediated immune response is a class I-restricted T cell response.

98. (Previously presented) The method of claim 95, wherein the cell mediated immune response is a class II-restricted T cell response.

REMARKS

Pending claims and request for clarification

Claims 54, 57-59, 61-69, and 88-98 were previously allowed in the present case (Notices of Allowance and Allowability were mailed and the issue fee was paid). However, a Notice of Withdrawal from Issue was subsequently mailed and, in the present Office action, the Examiner states that claims 54, 57-59, 61-64, 66, 68, 69, 88, 89, and 91-98 are now pending. Applicants respectfully disagree, as none of the previously allowed claims have been canceled. Applicants believe the claims now pending are the same as those previously allowed: claims 54, 57-59, 61-69, and 88-98. Applicants respectfully request confirmation.

Applicants thank Examiner Zeman for the helpful telephone interview she held on March 18, 2005, with Mr. Len Rasile, Dr. Lee Mizzen, and Applicants' representative, Lee Crews (the undersigned). The present rejection on the basis of obviousness was discussed, and the remarks that follow are consistent with that discussion.

35 U.S.C. § 103(a)

Young in view of Johansson

The Examiner states that "[c]laims 54, 59, 91, 91, 63, 64, 95, 96, 97, 98, 68, 69, 88, 89, 94, 61, 62, 92, and 93" are rejected as being obvious over Young (WO 94/29459; herein "Young") in view of Johansson *et al.* (*J. Infect. Dis.* 162:800-809, 1990; herein "Johansson"). As noted above, none of claims 65, 67, or 90 were listed as pending, nor are they listed as rejected here (in addition, the Examiner lists claim 91 twice). For the reasons stated above, Applicants believe claims 65, 67, and 90 are pending and request clarification as to whether or not these claims stand rejected over Young and Johansson or any other combination of references cited herein. Applicants note that claims 57, 58, and 66, all of which the Examiner recognizes as pending, are not rejected in view of Young and Johansson.

The Examiner characterizes Young as disclosing "fusion proteins of bacterial stress proteins with antigens, proteins or peptides" (Office action at page 2). The Examiner further notes Young's teaching that heat shock proteins fused to antigens can be produced recombinantly

(Office action at page 2 citing Young at pages 21-22). Young exemplified a fusion protein containing hsp70 and an HIV p24 antigen. As the Examiner acknowledged, "Young does not specifically disclose influenza antigens" (Office action at page 3). [1]

The Examiner characterizes Johansson as disclosing "purified neuraminidase [NA] vaccines for the induction of an immune response to the influenza virus" (Office Action at page 3). The Examiner further states (Office action at page 3):

> Johansson provides purified NA antigens for inoculation, and tests with viral challenge. The inoculation of the subjects with the NA vaccine results in the generation of a strong humoral response (antibodies to NA). The purified NA had superior NA immunogenicity in comparison to the whole virus vaccine.

The Examiner's conclusion is that "[i]t would have been obvious to one of ordinary skill in the art to have replaced the p24 antigen in the hsp70-p24 fusion protein of Young with the influenza NA antigen of Johansson et al." (Office action at page 3). The Examiner argues that the requisite motivation would have been one's desire to "provoke a response from both the humoral immune system, and the cellular immune system" because "[t]he most effective vaccines activate both parts of the immune system" (Office action at page 3). According to the Examiner, "Young discloses that the heat shock protein induces a clear T cell response to the antigen that is in fusion, and Johansson et al. disclose that influenza NA antigen can provoke a strong, humoral immune system response" (Office action at page 3). Regarding an expectation for success, the Examiner posits that, "in making the fusion construct between hsp70 and the influenza NA ... only routine cloning skill (*sic.*) are required" (Office action at page 3). The Examiner's final remark concerning this combination of reference is (Office action at page 3):

> Young provides the necessary hsp sequences and vectors, and Johansson et al. provide the influenza NA. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

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[1] As noted on the record, however, U.S. Patent No. 6,338,952, which issued from a corresponding U.S. application, discloses "Influenza virus Hemagglutinin" (see the Office action mailed June 4, 2002, at page 5).

This ground for rejection is respectfully traversed. One of ordinary skill in the art, upon reading Young and Johansson, would not have been motivated to fuse NA to an hsp. Young does state that his invention "relates to compositions comprising a stress protein joined to another component, such as a fusion protein in which a stress protein is fused to an antigen" (Young at pages 3-4) and Johansson does immunize mice with purified influenza NA. However, "[t]he consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process [the claimed invention] *should* be carried out ..." *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988) (emphasis added). "It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references." *Pro-Mold and Tool Co., Inc. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568 (Fed. Cir. 1996).

Here, there is no reason, suggestion, or motivation to lead one to an hsp-NA fusion protein. The Examiner states that one would want to provoke both the humoral and cellular immune systems because that is what the most effective vaccines do. However, one of ordinary skill in the art would recognize, just as the Examiner did, that Johansson immunized mice with purified NA and subjected those animals to a viral challenge; that inoculation of the subjects with the NA vaccine resulted in the generation of a strong humoral response; and that, in the long run (after a second viral challenge), the NA vaccine was superior to a whole virus vaccine (*see* the abstract). This was a welcome result because, as Johansson explained, "[w]ith NA vaccine as a prelude, concern about underattenuation or reversion of live virus vaccine to virulence would be obviated" (*see* the last sentence of the discussion). Thus, Johansson has found an improved vaccination scheme. There is nothing to suggest that the scheme should be changed to include an NA-hsp fusion protein rather than the purified NA that was used; the antibody response to purified NA was strong, and there is nothing in Johansson that suggests the need for a cellular immune response. Young demonstrates that a cellular immune response can be obtained with a

fusion protein containing an antigen or with the antigen alone. With the exemplified p24-hsp fusion protein, Young found that (page 23, lines 13-15):

> a demonstrable T cell response was seen in mice injected with the p24-hsp70 fusion protein and in mice injected with p24 alone.

Thus, neither Young nor Johansson teach that a cellular immune response is desirable or required in the context of influenza.

Moreover, even if there were some reason to modify Johansson's purified NA, the art of record suggests polymers of multiple antigenic determinants, not recombinant proteins. As noted in the Reply filed June 11, 2001, the art at the time the present application was filed suggested that recombinant proteins (which fusion proteins would necessarily be) are not as immunogenic as polymers of multiple antigenic determinants. In the background section of his U.S. Patent (No. 4,918,166), Kingsman states (emphasis added):

> A substantial disadvantage of most antigens produced by recombinant DNA techniques for vaccines is that they are usually made as simple monomeric proteins. This is not the ideal configuration for an immunising antigen as it does not readily permit the cross-linking of the components of the immune system that is required for maximum stimulation of humoral and cellular immunity. An ideal immunogen is a polymer of multiple antigenic determinants assembled into a high molecular weight carrier. A good immunogen should also have the maximum number [of] epitopes exposed. This is best achieved by presenting multiple copies of the antigen on the surface of a particle.

In view of the foregoing, it should be clear that when one of ordinary skill considered the data and other teaching of Young and Johansson, together with Kingsman and without the benefit of hindsight, there was no motivation to make the modification the Office describes. On that basis alone, the rejection for obviousness should be withdrawn.

Lastly, Applicants contend that all of the present claims are patentable because it was not obvious to select the influenza antigens now recited in those claims (nucleoprotein, neuraminidase, M1, M2, PB1, PB2, and PA). As noted on the record and described further below, the facts in the

present case are consistent with those in *in re Baird* 16 F.3d 380 (Fed. Cir. 1994), where the Federal Circuit found patentable subject matter.

Young and Fiers

"Claims 54, 59, 91, 91, 63, 64, 95, 96, 97, 98, 68, 69, 88, 89, 94, 61, 62, 92, 93 are rejected" as being obvious over Young in view of Fiers *et al.* (U.S. Patent No. 5,962,298; herein, "Fiers"). The same statements and requests made above regarding the claims apply here: claims 65, 67, and 90 should be pending; the Examiner lists claim 91 twice; and claims 57, 58, and 66 have not been rejected.

The Examiner characterizes Young as above and states that Fiers (Office action at page 4):

> Disclose purified neuraminidase vaccines for the induction of an immune response to the influenza virus. Fiers provides purified recombinant NA antigens for use as a vaccine. The inoculation of the subjects with the NA vaccine results in the generation of a strong humoral response (antibodies to NA), and protection against homologous challenge. The NA vaccine also provided strong partial protection to heterologous challenge. Passive transfer of serum from NA inoculated mice was also protective, indicating the bulk of the protective response was due to circulating antibodies to NA.

The reasoning upon which the Examiner's conclusion is based is the same as the reasoning used in connection with Young and Johansson: one would have been motivated to replace the p24 antigen of the hsp70-p24 fusion protein of Young with the influenza NA antigen of Fiers "to provoke a response from both the humoral immune system, and the cellular immune system" because "[t]he most effective vaccines activate both parts of the immune system" (Office action at page 4). One would have a reasonable expectation of success "as only routine cloning skill are (*sic.*) required" (Office action at page 4).

This ground for rejection is respectfully traversed. As the Examiner recognizes, Young does not disclose neuraminidase (NA) , as required by claim 54. To find that limitation, one must turn to Fiers, which, as the Examiner notes, provides purified recombinant NA antigens for use as a vaccine. Fiers concluded that, following immunization with NA, "precirculating NA antibodies are capable of

and sufficient for providing complete protection" (column 17, lines 1-3). Fiers also determined that the protective immune response is due to a humoral immune response. Fiers states (column 18, lines 22-26):

> Passive transfer of serum of mice which were immunized with NAs to naïve recipient mice resulted in the same levels of protection, which indicates that the protective effect of NAs immunization can be explained on the basis of circulating NA antibodies.

Thus, there is no motivation to make the substitution the Examiner suggests. Fiers' NA antigen works perfectly well as it is, and the antibodies generated afforded "complete protection." Thus, Young's suggestion that hsps stimulated a cellular immune response is irrelevant in this context. Fiers demonstrates that a cellular immune response is not required. As such a response is not required, there is no motivation to try to achieve it. As neither Young nor Fiers, alone or in combination, would motivate one to substitute NA for the p24 antigen in Young's fusion protein, this ground for rejection should be withdrawn.

Young and Paoletti

"Claims 54, 57, 58, 66, 59, 91, 91, 63, 64, 95, 96, 97, 98, 68, 69, 88, 89, 94, 61, 62, 92, [and] 93" are rejected as being obvious over Young in view of Paoletti *et al.* (U.S. Patent No. 5,174,993; herein, "Paoletti"). Here, all of the claims listed as pending on the Office Action Summary are rejected. The Examiner characterizes Young in the same manner as noted above (Office action at page 5) and characterizes Paoletti as follows:

> Paoletti et al. (US 5,174,993) disclose recombinant vectors comprising nucleoprotein (NP) for use in producing an immunological response. Paoletti provides recombinant avipox vectrs (*sic.*) which can comprise chicken nucleoprotein gene (col. 6) (among many others, including HA) which produce NA antigens for use as a vaccine. The vector used to clone the NP gene is called pNP33. The inoculation of the subjects with the avipox vaccine results in the generation of a strong humoral response, and protection against homologous challenge.

The Examiner's conclusion refers to the motivation to provoke both humoral and cellular immune responses and the routine level of skill required to make the fusion construct (Office action

at pages 5-6). Significantly, the Examiner also states "Young provides the necessary hsp sequences and vectors, and Paoletti et al. provide the influenza NP sequences" (Office action at page 6).

This ground for rejection is respectfully traversed. The present claims are patentable because it was not obvious to select the influenza antigens now recited in those claims (nucleoprotein, neuraminidase, M1, M2, PB1, PB2, and PA). While fusion proteins containing stress proteins are clearly disclosed by Young, this does not mean that Young -- even in combination with a secondary reference like Paoletti -- renders all fusion proteins obvious. Young's disclosure of this genus, even in combination with a secondary reference like Paoletti, cannot render obvious the specific fusion proteins now claimed. The genus-species relationship was addressed in view of the statutory requirement for non-obviousness in *In Re Baird, supra.* As discussed previously with Examiner Zeman in person (during the interview of October 25, 2001) and on the record (see the Reply filed February 28, 2002), the facts in the present case are consistent with those in *Baird.* Here, as in *Baird*, there is patentable subject matter.

Baird claimed a toner comprising a binder resin; the binder resin was a bisphenol A polyester, which could contain succinic acid, glutaric acid, or adipic acid. Baird's claims were rejected as being obvious over a single piece of prior art: a U.S. patent to Knapp, which disclosed "developer compositions" comprising a diphenol having a generic formula. Knapp also taught that succinic acid, glutaric acid, and adipic acid could be included. The Examiner argued that Baird's claims to bisphenol A were obvious because bisphenol A is produced when certain specific variables are selected for inclusion in Knapp's generic formula. The Examiner argued that bisphenol A could be easily derived from Knapp's generic formula, particularly since Knapp also described the required elements (succinic, glutaric, and adipic acid). The Board of Appeals and Patent Interferences affirmed the Examiner's rejection. Nevertheless, the Court of Appeals for the Federal Circuit found the subject matter covered by Baird's claims was non-obvious. The court found nothing in Knapp to suggest that one should ***select*** the variables required to produce bisphenol A.

The facts in the present case parallel those in *Baird*, and the conclusion here should be the same as that in *Baird*: non-obviousness. In fact, certain aspects of the present case provide

an even stronger basis for this outcome. For example, in *Baird* both the generic formula and the specific variables that, if chosen, would give rise to the compound claimed, were found within a single prior art reference (the Knapp patent). Here, one of ordinary skill in the art would have to look beyond Young, which fails to mention any of the specific influenza antigens now recited in the claims. The invention Baird claimed was found non-obvious because there was no suggestion in Knapp to select bisphenol A from the vast number of diphenols covered by the generic formula. The present Applicants make the same argument: there is no suggestion in Young, or in the combination of Young and Paoletti, to select nucleoprotein, neuraminidase, M1, M2, PB1, PB2, or PA from the vast number of antigens that could be included in a stress protein-containing fusion protein. In accordance with the law on obviousness, this ground for rejection should be withdrawn.

Here, too, the prior art fails to teach the desirability of a cellular immune response.

Young and Kendal

"Claims 54, 59, 91, 91, 63, 64, 95, 96, 97, 98, 68, 69, 88, 89, 94, 61, 62, 92, [and] 93" are rejected as being obvious over Young in view of Kendal *et al.* (U.S. Patent No. 5,290,686; herein, "Kendal"). Applicants queries as to the claims pending and rejected are as stated above. The Examiner characterizes Young as in the preceding grounds for rejection (Office action at page 6) and characterizes Kendal as follows (Office action at pages 6-7):

> Kendal et al. (US 5,290,686) disclose recombinantly expressed influenza M2 proteins for the induction of an immune response to the influenza virus. Kendal provides baculovirus expressed M2 antigens, and indicates that the M2 protein is a target of the immune system in influenza infection. The M2 protein has a lower rate of antigenic drift than other influenza proteins, and is therefore a good candidate for use in vaccines. Kendal notes that mice inoculated with monoclonal antibodies to M2 were partially protected against viral challenge. Infected human sera also produces antibodies to M2, indicating that M2 antigens provoke the humoral immune system.

The Examiner then argues, for the same reasons relied on in making the rejections above, that it would have been obvious to replace the p24 antigen in the hsp70-p24 fusion protein of Young with the influenza M2 antigen of Kendal (Office action at page 7).

This ground for rejection is respectfully traversed. There is no more motivation to select M2 or to combine Young with Kendal than there is to select any of the other influenza antigens described in the prior art or to combine Young with Johansson, Fiers, or Paoletti. There is no evidence of record that the influenza antigens are deficient in some way that would be cured by inclusion in a fusion protein with an hsp, there is no teaching regarding the desirability of a cellular immune response, and there is no motivation to *select* the antigens now recited in the claims. The large genus of fusion proteins disclosed by Young, even when considered in combination with a secondary reference such as Kendal, does not render obvious the specific fusion proteins now claimed. This ground for rejection should be withdrawn.

Young and Parkin

"Claims 54, 59, 91, 91, 63, 64, 95, 96, 97, 98, 68, 69, 88, 89, 94, 61, 62, 92, [and] 93" are rejected as being obvious over Young in view of Parkin *et al.* (U.S. Patent No. 5,690,937; herein, "Parkin"). Applicants queries as to the claims pending and rejected are as stated above. The Examiner characterizes Young as in the preceding grounds for rejection (Office action at pages 7-8) and characterizes Parkin as follows (Office action at page 8):

> Parkin et al. (US 5,690,937) disclose recombinant PB2 antigens for the induction of an immune response to the influenza virus. Parkin et al also disclose PB1, PA and NP genes of influenza and note their importance in infection, and resulting attraction as a vaccine. Parkin provides the sequences of the PB2 gene, as well as a variety of temperature sensitive mutations of the PB2 gene. M and NP sequences are also disclosed. Routine cloning methods are used to produce recombinant PB2 proteins. Recombinant viruses comprising the variously described proteins are to be used as vaccines.

The Examiner then argues, for the same reasons relied on in making the rejections above, that it would have been obvious to replace the p24 antigen in the hsp70-p24 fusion protein of Young with the influenza PB2 antigen of Parkin (Office action at page 8).

This ground for rejection is respectfully traversed. There could have been no more motivation to select PB2 (or any other antigen disclosed by Parkin) than there would have been to select any other influenza antigen described in the prior art. There could have been no more motivation to combine Young with Parkin than there was to combine Young with Johansson, Fiers, Paoletti, or Kendal. As noted, there is no evidence of record that the influenza antigens are deficient in some way that would be cured by inclusion in a fusion protein with an hsp (and Kingsman teaches away from that construct). The large genus of fusion proteins disclosed by Young, even when considered in combination with a secondary reference such as Parkin, does not render obvious the specific fusion proteins now claimed. This ground for rejection should be withdrawn.